A Pharmacological Basis for Some Bad LSD Trips?: A 50+ Year Odyssey (Nichols et al., 2026)

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Background: In 1984, early clinical researcher Daniel Freedman noted that the clinical effects of LSD occurred in two temporal phases: an early psychedelic phase, followed later by a paranoid phase. Freedman drew parallels between this later phase and amphetamine psychosis in humans. Later, Mittman and Geyer (1991) showed that behavior acutely induced by LSD in rats also occurred in two temporal phases: an initial suppression of behavioral responding, followed by a subsequent increase in locomotor activity that is not observed with other serotonergic agonists.

Purpose: To test the hypothesis that the later “paranoid” phase of LSD intoxication is due to the formation of a metabolite of LSD. In particular, 13- and 14-hydroxy-LSD have been identified as minor metabolites in several animal species and in man.

Results: In a series of two-lever drug discrimination experiments in rats, it was found that testing the rats 30 minutes after administration of LSD generated an interoceptive cue that was mediated by serotonin 5-HT2A receptor activation. However, when testing was delayed until 90 minutes after LSD administration, a time-dependent cue was generated that was mediated by dopamine D4 receptor activation, as determined through the use of highly selective receptor antagonists. Synthesis and in vitro receptor testing of 13- and 14-hydroxy-LSD at the human dopamine D4 receptor demonstrated that 13-hydroxy-LSD was 380 times more potent as a dopamine D4 agonist than LSD, with a 36 picomolar (36 x 10-12 M) potency (EC50), whereas LSD itself had a 14 nanomolar (14 x 10-9 M) EC50. Thus, 13-hydroxy-LSD may be the most potent dopamine D4 agonist yet discovered. Surprisingly, a clinical trial of a highly selective dopamine D4 antagonist, Sonepiprazole, had no efficacy in a clinical trial in schizophrenia.

Conclusion: Although 13-hydroxyLSD is only a very minor metabolite of LSD, with such high potency at the dopamine D4 receptor, only a tiny amount would be necessary to affect behavior. The normal function of the dopamine D4 receptor remains largely unknown. These experiments argue that the importance of the D4 receptor deserves more intense study.

A Pharmacological Basis for Some Bad LSD Trips?

(A 50+ Year Odyssey)

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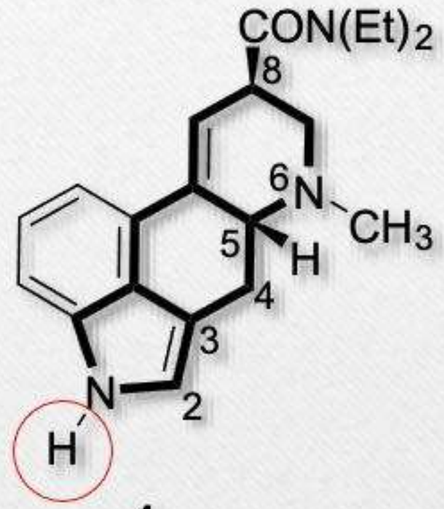
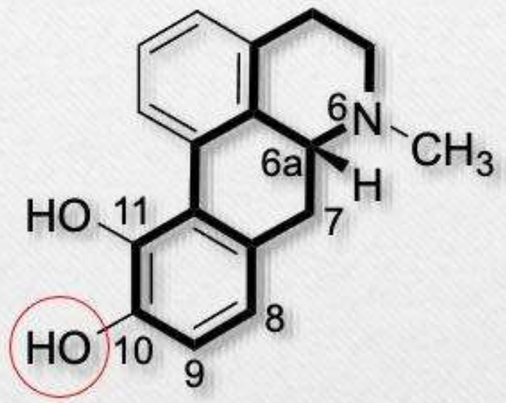
Ergolines Possess Dopaminergic Activity

Nichols **(1976)** noted the potential importance of the dopaminergic properties of LSD, the effects of which had largely been ascribed to serotonergic actions. Below is a reproduction of Figure 3 from that publication:



1



3

The indole NH of LSD would be a hydrogen bond donor to a residue within the dopamine receptor.

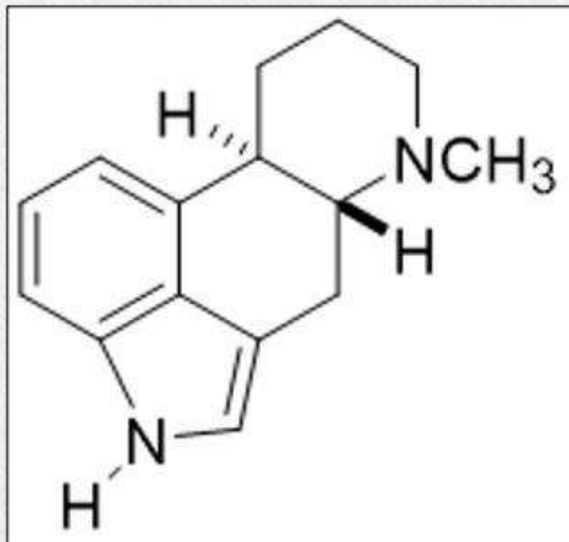
Synthesis and testing of 6aS-(+)-10,11-dihydroxyaporphine, the enantiomer of apomorphine (Saari, King & Lotti, 1973) demonstrated that only the 6aR-(-) isomer, shown above, derived from natural morphine, possessed dopaminergic activity.

Ergoline Fragments Possess Dopaminergic Activity

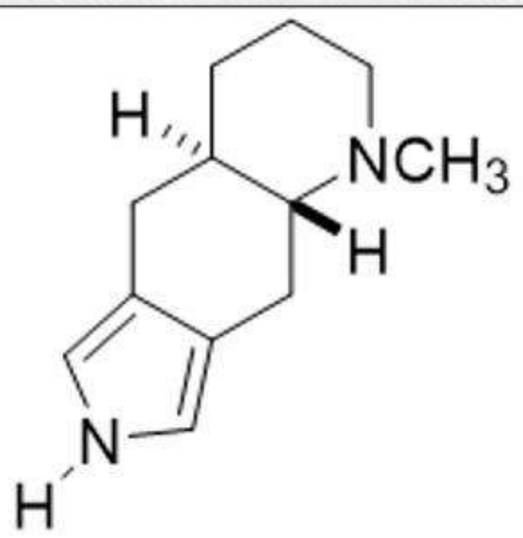
Ed Kornfeld wrote to DEN in 1977, indicating the Eli Lilly group had come to a similar conclusion.

The first paper in the Lilly series, by Bach et al. **(1980)**, measured **suppression of serum prolactin** in reserpinized male rats, as an indication of dopamine receptor stimulation.

They showed suppression of prolactin for the following illustrative compounds:

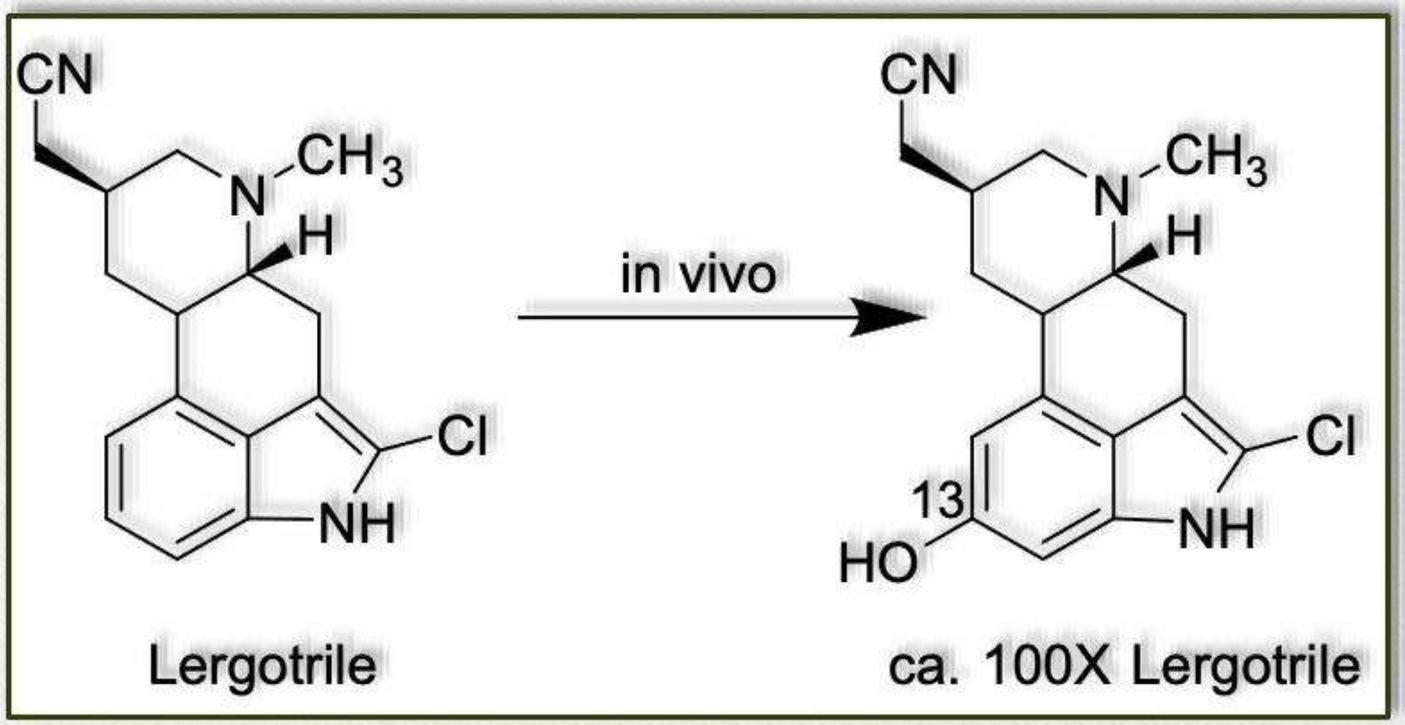


91% @ 5 mg/kg



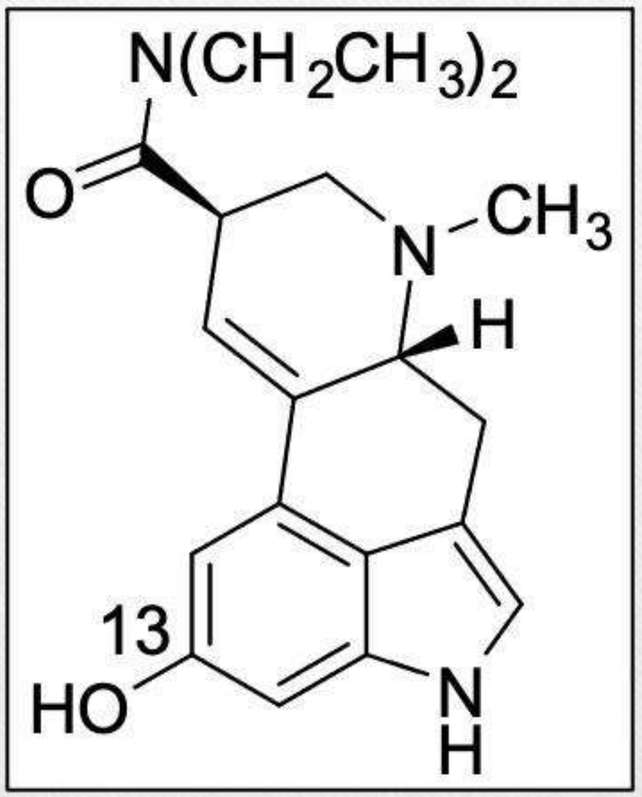
90% @ 5 mg/kg

13-Hydroxylergotrile is approximately 100 times more potent than lergotrile itself



Parli et al. (1978):

13-Hydroxy-LSD is a metabolite of LSD in the rat, guinea pig, and rhesus monkey



Siddik et al. (1975,1979)

LSD Can Have Time-Dependent Effects in Humans

Pioneer clinical LSD researcher Daniel X. Freedman wrote a book chapter in which he described the clinical effects of LSD as occurring in two temporal phases (Freedman, 1984):

1. A *"psychedelic experience"* in the early phase, with *"meaningfulness and portentousness"* as the prime characteristics, and,
2. A second phase that is "*clearly a paranoid state*." He noted that this latter phase develops about 4-6 hours after LSD administration. At times out to 10 hours post-drug, subjects given LSD *"...regularly report... they had been at the least self-centered, and usually suspicious, with ideas of reference or even paranoid convictions."*

Freedman drew parallels between this later phase and amphetamine psychosis in humans and emphasized the possibility that *clues to understanding psychosis might be found in this "paranoid" phase of LSD intoxication*.

Freedman 1984

Similarly, behavior acutely induced by LSD in rats occurs in two temporal phases:

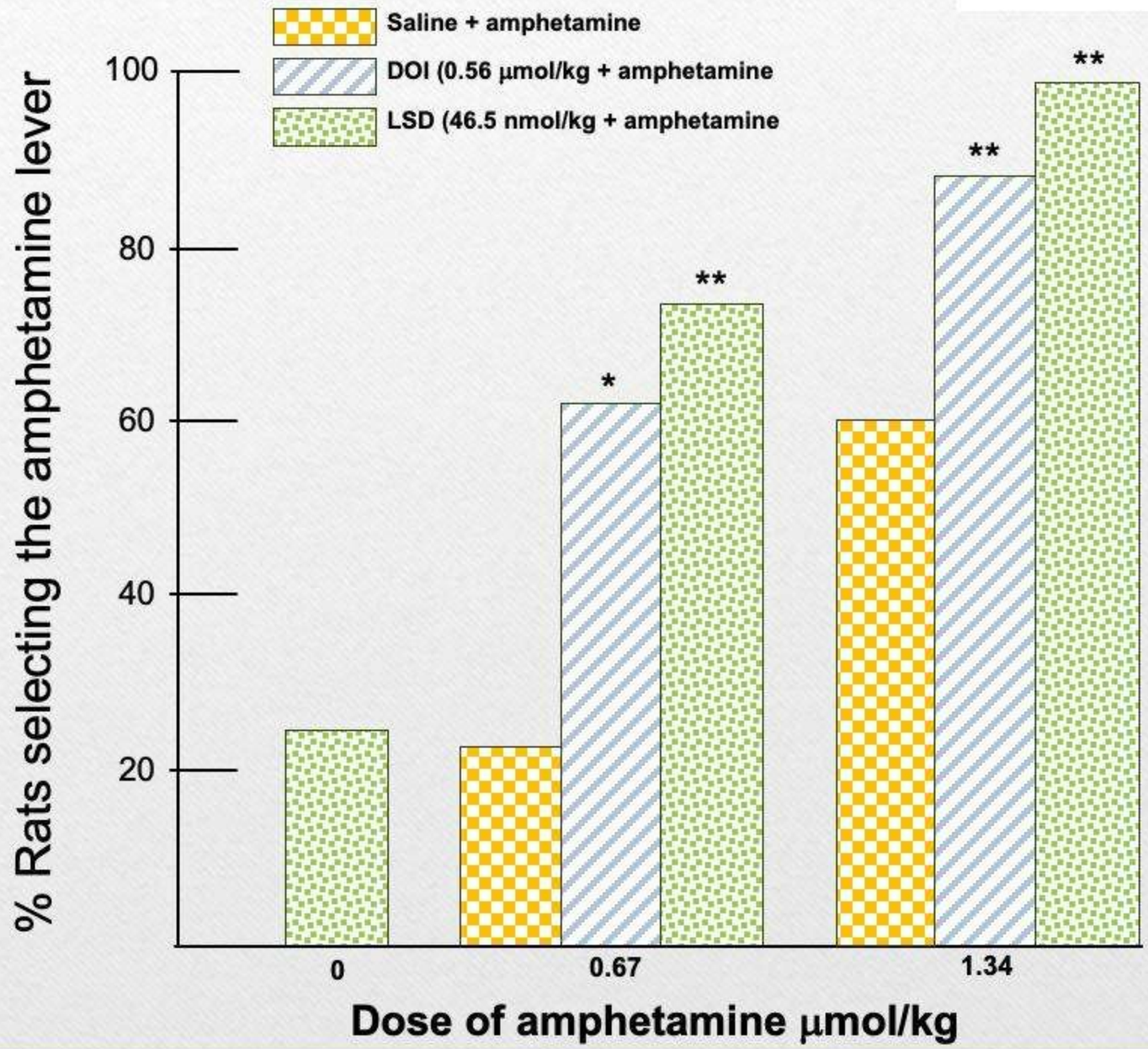
1. Initial suppression of behavioral responding, followed by,
2. A subsequent increase in locomotor activity that is not observed with other serotonergic agonists (e.g. DOI).

Do the serotonergic actions of LSD potentiate its inherent dopaminergic activity?

Mittman and Geyer (1991)

If rats trained to discriminate 1 mg/kg (5.4 mmol/kg) amphetamine sulfate are pretreated 2 or 3 hours with LSD or DOI, their response to amphetamine is significantly potentiated.

Marona-Lewicka et al. (1997)

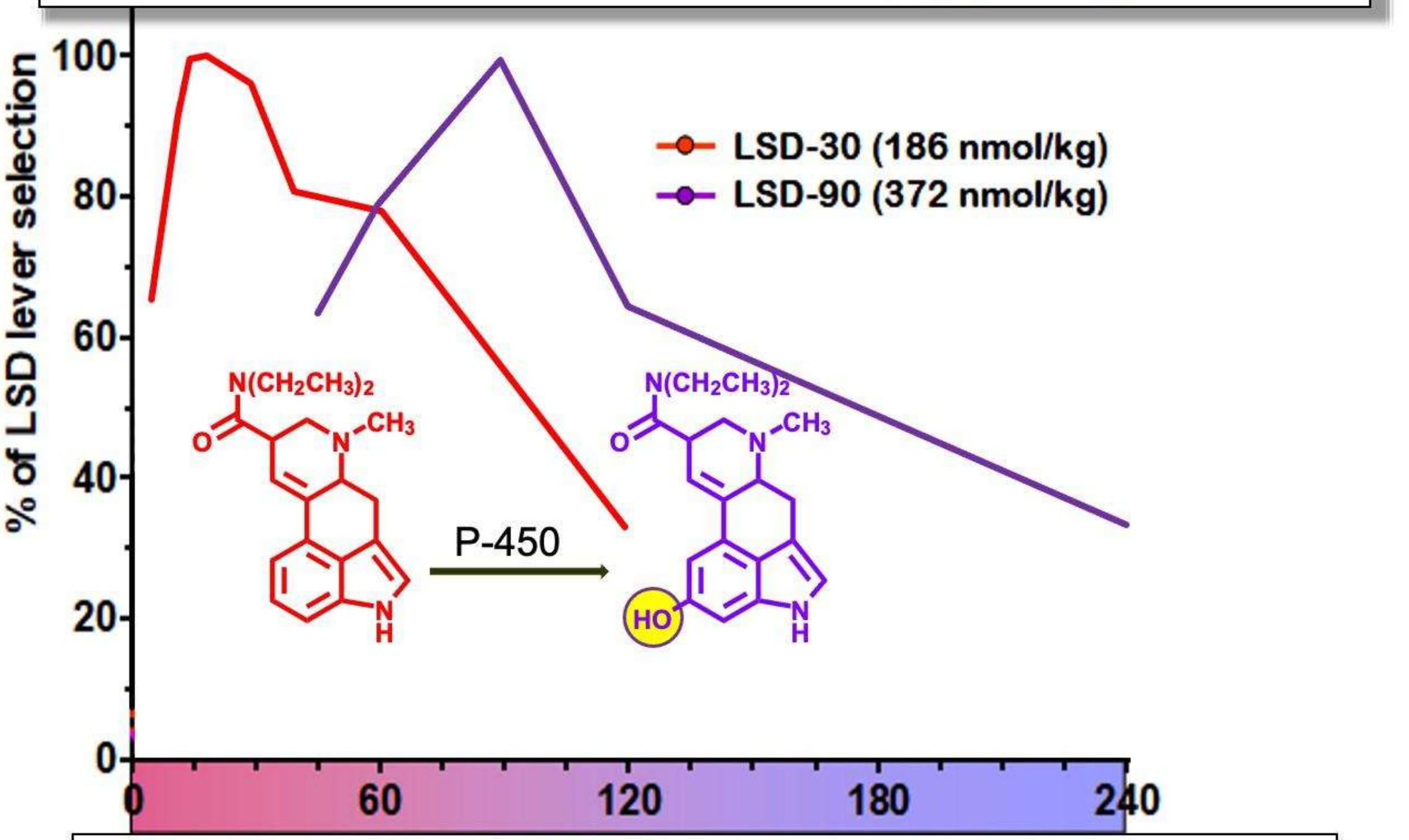


Does LSD evoke a serotonin 5-HT2 receptor-mediated sensitization of dopamine D2/3 receptors

Minuzzi et al. (2005) used PET to examine the effects of LSD on D2/3 receptor binding by [^{11}C]-raclopride in the living pig brain. They observed an unusual progressive displacement of the PET ligand that only reached a maximum four hours after LSD administration….

But…. This phenomenon would also be consistent with the formation of an LSD metabolite that had exceptionally high affinity for D2/3 receptors.

LSD Discrimination in Rats Indicates 5-HT2A Mediation of the Cue at 30 min after 372 nMol/kg (LSD30), but Dopamine D4 Mediation of the Cue after 90 minutes also at 372 nMol/kg (LSD90).



Marona-Lewicka et al., 2005, Marona-Lewicka & Nichols 2007, 2009

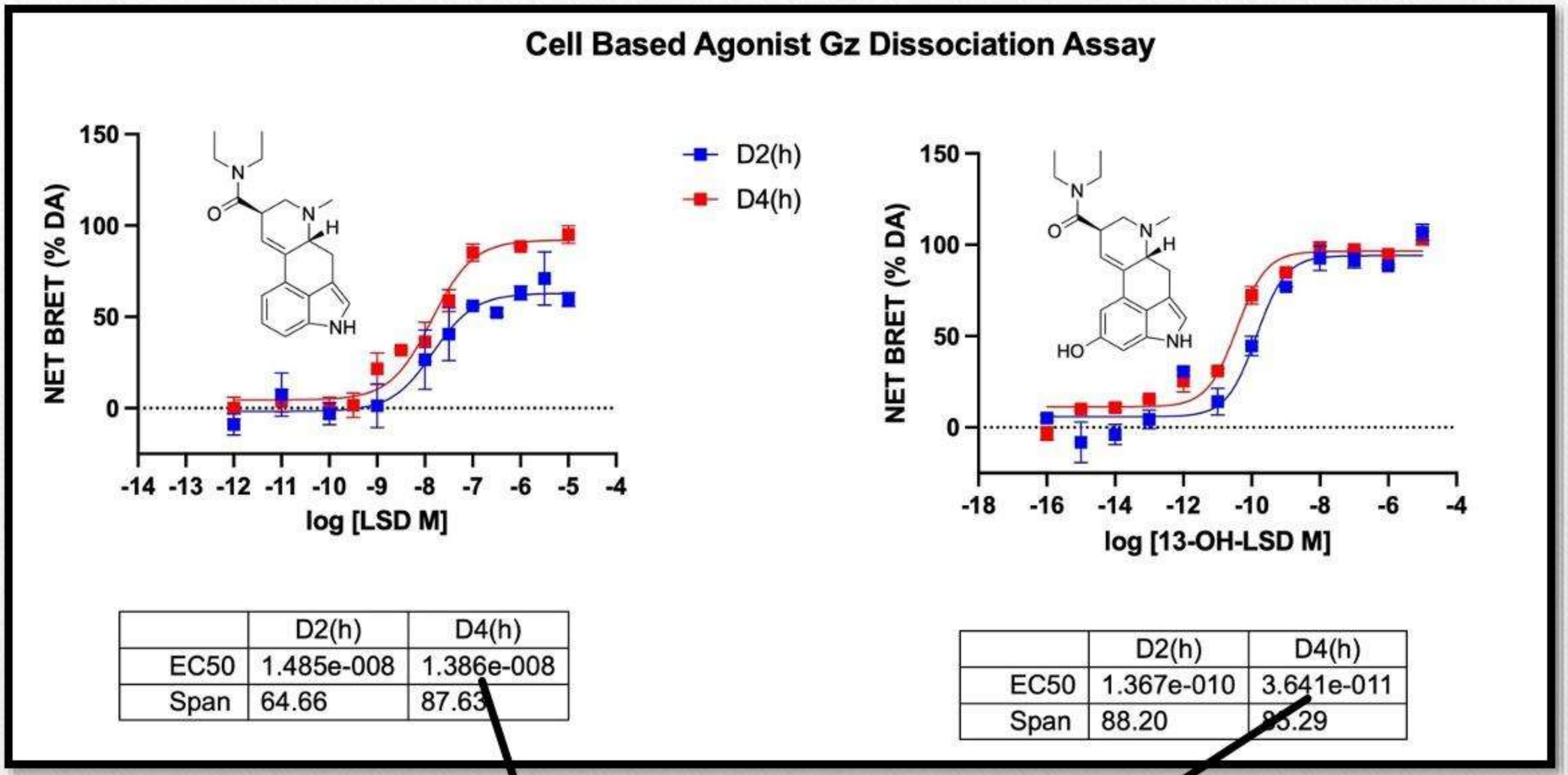
More Recent Evidence for the Formation of Hydroxy-LSD metabolites in humans:

Canezin, Cailleux et al. 2001, both 13- and 14-hydroxy LSD glucuronides in human urine.

Dolder et al 2018 13- and 14-hydroxyLSD could be detected sporadically at very low levels.

Are Hydroxy-LSD metabolites in humans physiologically relevant?

13-OH-LSD is 382x more potent at D4R than LSD!



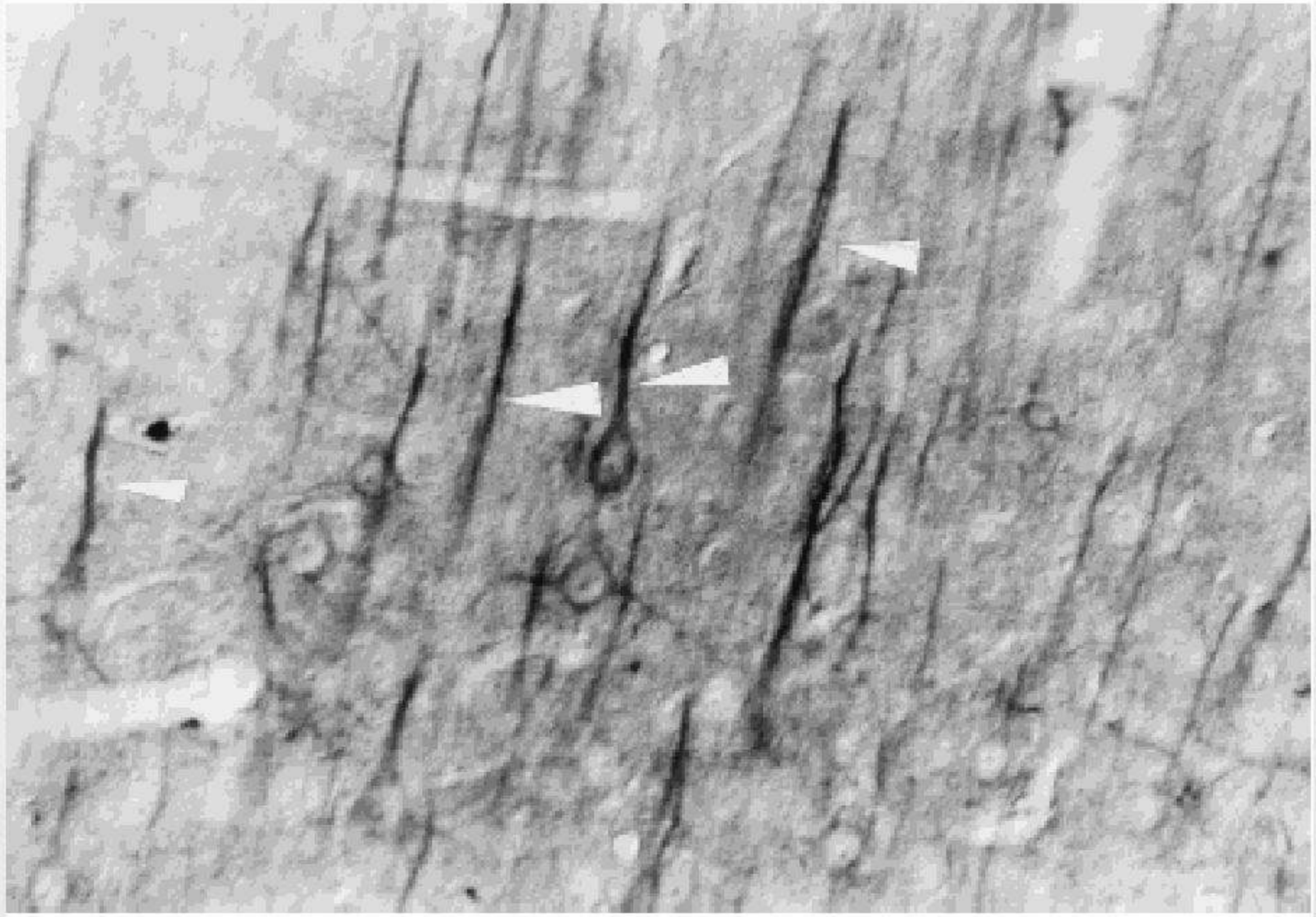
	D2(h)	D4(h)
EC50	1.485e-008	1.386e-008
Span	64.66	87.63

	D2(h)	D4(h)
EC50	1.367e-010	3.641e-011
Span	88.20	85.29

1.39e-008/3.64e-011= **382**

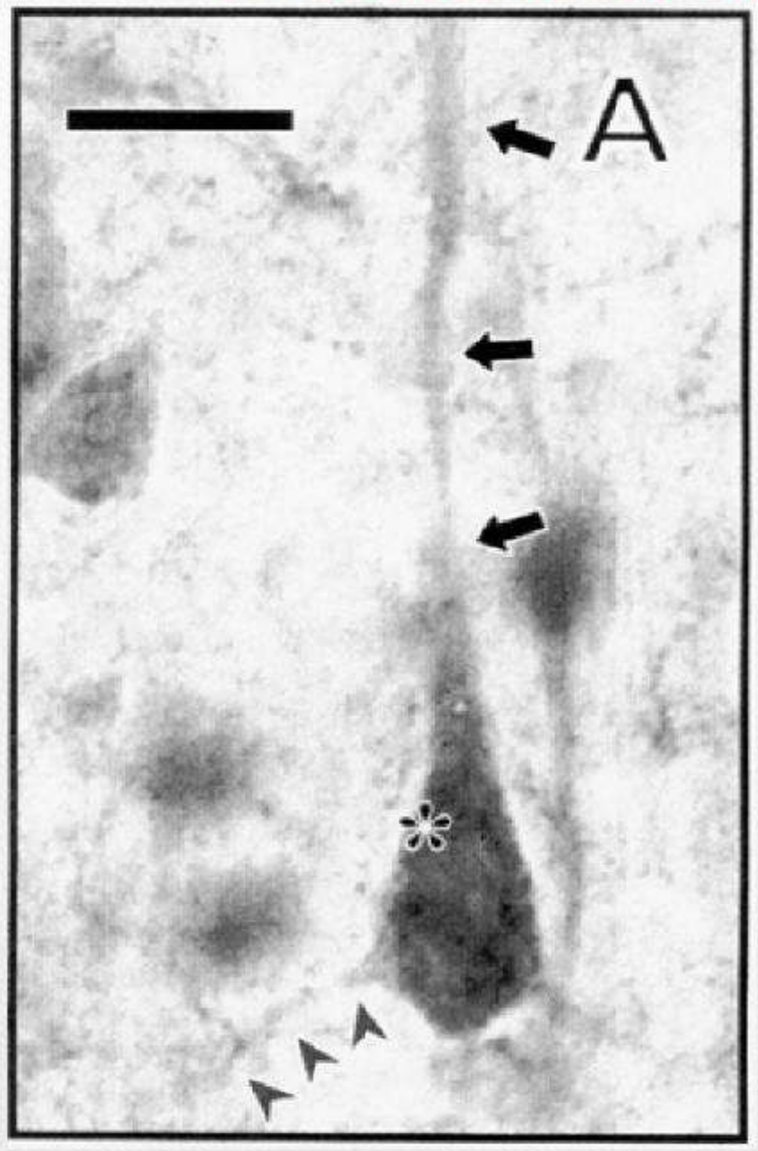
1.49e-008/1.67e-010= **89.2**

5-HT2A immunoreactivity (arrowheads) on apical dendrites of pyramidal cells in rat cortex

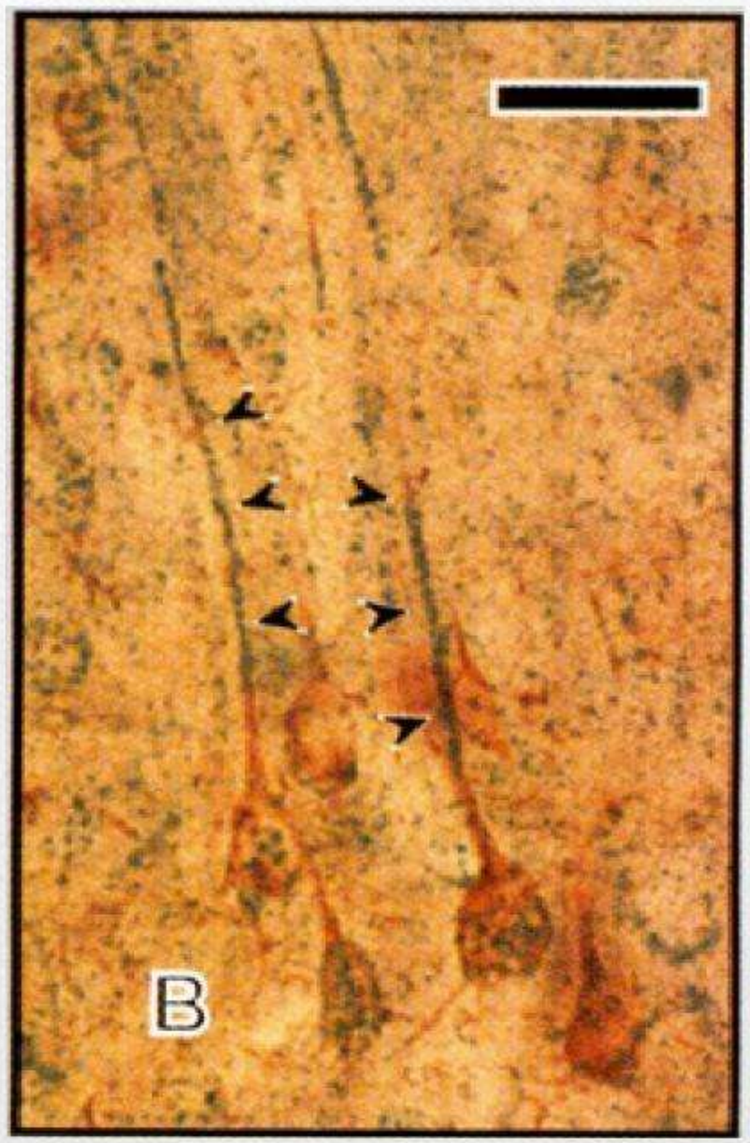


Willins et al., Synapse 1997

Dopamine D4 Receptors also on Apical Dendrites of Cortical Pyramidal Cells



D_4-positive neuron in rat parietal cortex (layer V). Arrowheads show faint staining of basilar dendrites. Arrows show dendritic processes with D_4 immunoreactivity.



Colocalization of D_4 receptors (arrowheads; blue) with nonphosphorylated neurofilament H-positive (brown) neurons in rat cingulate cortex.

Wedzony et al. J. Physiol. Pharmacol. 2000, 51, 205-221

Sonepiprazole, a highly selective D4 antagonist had no efficacy in a clinical trial in schizophrenia (Corrigan et al. 2004).

Conclusion:

Further study of the role of the D_4 dopamine receptor in brain function is warranted.

Support:

Early studies by NIDA DA 02189 (DEN).

Recent studies by 2A Biosciences.